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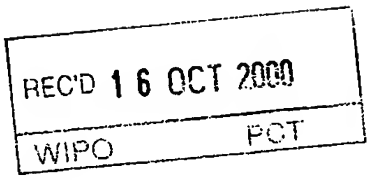

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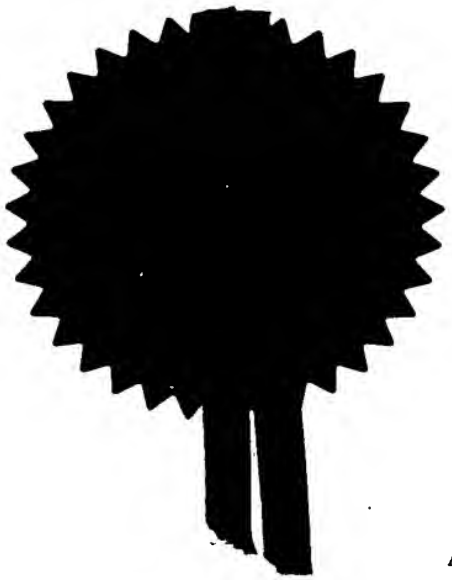

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Dated 09 OCT 2000

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P01/7700 0.00 - 9923431.2

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1. Your reference — P.75428A GCW/RCS

2. Patent application number *(The Patent Office will fill in this part)* — **9923431.2** — -4 OCT 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CARTER, John
246 Kenton Road
Harrow
Middlesex
HA3 8BY

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — 66w3068001

4. Title of the invention — PHARMACEUTICAL COMPOSITIONS AND THEIR USE

5. Name of your agent *(if you have one)* — J A KEMP & CO

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

14 SOUTH SQUARE
GRAY'S INN
LONDON WC1R 5LX

Patents ADP number *(if you know it)* — 26001

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Number of earlier application	Date of filing *(day / month / year)*

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11. I/We request the grant of a patent on the basis of this application

Signature J.A. Kemp & Co Date 4 October 1999

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PHARMACEUTICAL COMPOSITIONS AND THEIR USE

This invention relates to pharmaceutical compositions and their use in the treatment of neoplastic disease.

There has long been a demand for a safe and effective treatment of neoplastic disease. WO 84/04922 proposes the use of copper salicylate complexes for this purpose. However, the copper salicylate complexes of WO 84/04922 are not sufficiently effective to be put to widespread use.

It has now unexpectedly been discovered that a composition comprising an assimilable copper compound, a source of salicylic acid or a derivative thereof, and one or both of an assimilable manganese compound and vitamin C, is particularly effective in the treatment of neoplastic disease.

The present invention therefore provides a composition comprising:

(a) a physiologically acceptable source of assimilable copper;

(b) a source of salicylic acid or a physiologically acceptable derivative thereof; and

(c) vitamin C and/or a physiologically acceptable source of assimilable manganese.

The composition of the present invention contains vitamin C and/or a physiologically acceptable source of assimilable manganese. Addition of one or both of these ingredients to components (a) and (b) leads to a dramatic increase in effectiveness. It is preferred that the composition of the invention comprises both the physiologically acceptable source of assimilable manganese and the vitamin C.

It has also unexpectedly been found that compositions of the invention further comprising a physiologically acceptable source of assimilable zinc are particularly effective in the treatment of sarcomas.

The present invention therefore also provides a

composition of the invention, further comprising a physiologically acceptable source of assimilable zinc.

The sources of copper, manganese and zinc used in the compositions of the present invention preferably contain the metals in ionic form, e.g. as salts with organic or inorganic acids. However, other metal compounds which provide assimilable sources of the metals, e.g. metal oxides, can also be used. Suitable physiologically acceptable salts of the metals are the salts with orotic acid, aspartic acid, gluconic acid, tartaric acid, citric acid, lactic acid or acetic acid. Suitable physiologically acceptable salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, hydriodic acid, phosphoric acid or sulphuric acid. Such salts are available commercially or may be prepared if desired by known methods. Salts of the metals with organic acids, especially orotic acid, are preferred. When, as is preferred, the compositions of the invention contain more than one metal, all the metal salts preferably include the same anion.

The compositions of the invention include a source of salicylic acid or a physiologically acceptable derivative thereof in which the carboxyl or hydroxyl function of salicylic acid has been converted into a derivative. Samples of suitable derivatives include metal salts such as sodium or potassium salicylate, esters such as methyl or ethyl salicylate, and amides such as salicylamide. Derivatives in which the hydroxyl function of salicylic acid has been converted into a derivative such as an ester, as in acetyl-salicylic acid (aspirin), can also be used. A particularly preferred derivative of salicylic acid is sodium salicylate. Salicylic acid itself and suitable derivatives of it are commercially available.

Components (a) and (b) may be present in the composition of the invention as a copper salicylate complex. As used herein, a copper salicylate complex is a

complex of copper and salicylic acid or a complex of copper and a said physiologically acceptable derivative of salicylic acid.

Preferably, vitamin C is present in the compositions of the invention in an amount significantly larger than what is regarded as the normal minimum daily requirement for an adult.

The compositions of the invention typically comprise 15 to 60, preferably 25 to 50, parts by weight copper orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper orotate is used.

Typically, the compositions of the invention comprise from 300 to 600, preferably 300 to 500, parts by weight, sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used.

Typically, the compositions of the invention comprise from 15 to 60, preferably 25 to 50, parts by weight manganese orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese orotate is used.

Typically, the compositions of the invention containing zinc comprise from 15 to 60, preferably 25 to 50, parts by weight zinc orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc orotate is used.

Typically, the compositions of the invention comprise from 200 to 1000, preferably 400 to 800, parts by weight vitamin C.

The parts by weight referred to are based on the total weight of these ingredients in the composition.

The proportions of the active ingredients in the compositions of the invention should be calculated having regard to the intended dosage to be administered. When the

composition is to be administered orally, as is usual, a suitable dosage is about 15 mg of copper orotate for each 60 lbs of body weight of the subject to be treated administered up to three times a day. The amount of manganese orotate administered is typically about the same. If present, zinc orotate is typically present in about half the amount of the copper orotate.

An appropriate proportion of salicylic acid or derivative thereof is about 200 mg and an appropriate proportion of vitamin C about 150 mg. These figures are approximate and considerable variation in the proportions of the active ingredients is possible without losing the valuable properties of the compositions.

The compositions of the invention may be made by first forming an intimate mixture of the metals to be used in the form of suitable salts or other derivatives. This mixture in finely ground form is then added to an aqueous solution or suspension of the salicylic acid or derivative thereof. Typically, from 2 to 5 ml, preferably about 3½ ml of aqueous solution or suspension is used. This solution preferably contains 5-20%, preferably about 10%, by weight of salicylic acid or derivative. The vitamin C may be added before or preferably after the salicylic acid solution. The resulting slurry may be administered orally.

The compositions of the invention are thought to work by promoting the formation of the enzyme superoxide dismutase (SOD). SOD functions as a free radical scavenger and reduces DNA damage caused by free radical attack.

The compositions of the invention may be used in human and veterinary medicine, for example in the treatment of cats and dogs. They are useful in the treatment or prevention of a neoplastic disease. They are capable of improving the condition of a patient suffering from a cancer.

Typically, a human or animal is treated by initially administering a first dose of 2 ml of the composition of

the invention, in the form of an aqueous suspension, per 60 lbs body weight of subject followed by half that dose 1 to 2 hours later. Four hours later a further half dose may be given. Subsequent treatment (when the tumour has noticeably regressed and/or the symptoms have been considerably alleviated) may consist of the oral administration of 2 ml of the suspension per 60 lbs body weight of subject once a day. This may be given for three weeks, then, if further progress has been made, the dose, may be reduced to 2 ml per 60 lbs body weight on alternate days for 3 weeks. The frequency of dosing may be further reduced as further progress is made.

The compositions of the invention have been found effective in treatment of carcinomas of the breast, rectum, bladder, liver, peritoneum, stomach and urethra, and in some lymphomas. Compositions of the invention comprising a physiologically acceptable source of assimilable zinc are effective against sarcomas. The treatment may be continued until there is a marked regression in the size of the tumour or until the tumour disappears.

The compositions of the invention are normally administered orally. Preferably, therefore they are suitable for oral administration. However, other routes of administration may be possible provided suitable precautions are taken to make the compositions suitable for administration in the contemplated way. Other forms suitable for oral administration may also be made, for example, tablets or capsules.

It has been found that the effectiveness of the compositions of the invention can be enhanced if they are administered in conjunction with a dietary regime which is low in salt and high in potassium and essential amino acids such as proline, serine, glutamine, lysine, histidine, alanine, methionine and leucine. By way of example, vegetables and fruit may be mentioned as foods which have high potassium content. Porridge oats, for example, have a

high potassium, low salt content. By way of example, liver may be mentioned as a food source rich in essential amino acids. Typically, for a human patient about 2 oz of liver per day has been found to be sufficient.

It has been found also that better results are obtained by supplementing the diet of a subject with additional vitamin C, i.e. vitamin C in addition to that preferably contained in the compositions of the invention. For example, the administration of 1 g of vitamin C per 20 lbs subject body weight per day, has been found to enhance the activity of the new compositions. Likewise, administration of nicotinic acid, for example 25 mg per 14 lbs subject weight per day, has been found to give rise to improved activity of the compositions of the invention.

The following Examples illustrate the invention.

EXAMPLE 1

Copper (II) orotate, 35 mg, and manganese (II) orotate, 35 mg, in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (800 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 2

Copper (II) orotate (35 mg), manganese (II) orotate (35 mg) and zinc orotate (35 mg) in finely divided form were mixed dry. 3.5 ml of a 10% aqueous solution of sodium salicylate (i.e. 3.5 ml of an aqueous solution containing 350 mg sodium salicylate) was then added followed by vitamin C (400 mg). The resulting suspension is suitable for immediate oral administration.

EXAMPLE 3

This experiment was conducted at University College London under Home Office License. In this experiment 100 C57B1 male mice were injected subcutaneously with a transplantable RMA thymoma tumour. 50 of the mice were used as controls and 50 mice were experimental mice.

Mice have a much faster rate of metabolism than larger mammals. It was therefore decided to give the mice a larger dose of the formula than the dose which would be suitable for larger animals such as cats and dogs. This latter dose was accordingly increased by a factor of 10.

For a 30 g mouse, 0.022 ml of the solution prepared in Example 1 was administered. This was administered to the mice three times a day at 10 am, 3 pm and 6 pm. The composition was administered by gavage. In addition the experimental mice were fed on a diet of organic wheat, barley, oats and rye.

The general condition of the experimental and control

mice following tumour injection is shown in Table 1.

Table 1

RMA thymoma in C57B1 male mice		
Days after Tumour injection	**Control**	**Experimental**
16	All mice have tumours. 2 killed because of large tumour size.	20/22 with palpable tumours. 2 probably have deep tumours. 1 sick mouse killed.
18		3 mice died as a result of treatment. 2 with small tumours. 1 had only a large lymph node.
20	4 mice killed with large tumours.	2 sick mice killed, both had tumours.
21	Remaining mice killed because of large tumours. All tumours firm and infiltrating muscle of thigh or peritoneal wall.	4 killed with large infiltrating tumours.
23		3/12 mice had superficial freely mobile plaque like tumours.
25		6 mice killed because of large tumour size. All tumours firm and infiltrating. 1 mouse had an axillary abscess.
29		4/6 remaining tumours fixed. Large lymph nodes palpable.
31		Remaining mice killed. 5/6 tumours infiltrating deeply. 1/6 more superficial but draining node grossly enlarged.

The growth of the tumour in experimental and control mice is shown in Figure 1. The weights of the experimental and control mice are shown in Figure 2.

The growth of the thymoma tumour was measured by callipers, i.e. the diameter of the surface of the tumour was determined. The tumours were not weighed at the end of the experiment.

As can be seen from Figure 1, 21 days after tumour injection the tumours in the control mice were approximately 1.9 times larger than those in the experimental mice.

Apart from deaths caused by the stress of gavage, to which the control mice were not subjected, the only side effect observed was slight weight loss, probably attributable to the change of diet.

EXAMPLE 4

This experiment was conducted at University College London under Home Office License. Transplantable mammary carcinomas were injected into 100 male Balb/c mice. 50 of the mice were used as controls and 50 mice were experimental mice.

These tumours grew much more slowly than the thymomas injected in Example 3. Accordingly, less treatment was given to the experimental mice; they were gavaged only once a day with 0.22 ml of the solution prepared in Example 1 and fed on a diet of organic grains as described in Example 3. Nevertheless a result was obtained as can be seen from Figure 3 showing the growth of the mammary carcinoma in experimental and control mice. But because they were given less treatment the difference in growth rate between the experimental and control groups is much less than that observed in Example 3.

The tumours in the control group were only 1.14 times larger than in the experimental group at 23 days after tumour injection. However, 29 days after tumour injection

the tumours in the control group were 1.19 times larger than the tumours in the experimental group.

Apart from deaths caused by the stress of gavage, to which the control mice were not subjected, the only side effect observed was slight weight loss, probably attributable to the change of diet.

EXAMPLE 5

Professor Peter Beverley of the Department of Oncology at University College London Medical School stated that although there was a statistically higher significant effect in tumour growth between the experimental and control mice in Examples 3 and 4, it was clear that the treatment by repeated gavage was stressful so that untreated mice were not a perfect control.

It was therefore decided that a further experiment should be performed but that this time the formula should be administered in the drinking water and given to the mice by gavage only once a day. As a water soluble copper salt was required for addition to the drinking water, it was decided to use copper gluconate in place of copper orotate. The control mice would also have the same organic grains diet as the experimental mice and be gavaged with water once a day. It was also decided that the experimental mice should be given extra vitamin C by having the vitamin C added to their drinking water.

This experiment was conducted at University College London under Home Office License.

Copper (II) gluconate, 35 mg, and manganese (II) orotate, 35 mg, in finely divided form were mixed dry. Sodium salicylate solution (3.5 ml of a 10% aqueous solution) was then added followed by vitamin C (800 mg).

The vitamin C was added to the drinking water of the experimental mice by putting 300 mg of vitamin C in 50 ml of water three times a day. Thus each cc contained 6 mg vitamin C. Each mouse drank on average 4 ml of water

containing 24 mg of vitamin C three times a day. So each mouse received on average 72 mg of vitamin C per day.

50 C57B1 male mice were injected subcutaneously with a transplantable thymoma. 24 mice, the experimental mice, were treated, and 26 mice were used as a control.

It was decided to give the mice a larger dose of the formula because they would be gavaged only once a day and it was not sure how much drinking water each mouse would drink.

The dose per mouse compared to larger mammals was now increased by a factor of 17.

Each mouse was gavaged with 0.04 ml of the composition prepared above once a day.

0.5 ml of the composition prepared above was added to the drinking water three times a day. 50 ml of drinking water was provided three times a day. 0.5 ml in 50 ml is 0.01 ml per cc. Each mouse drank approximately 4 ml of water three times a day so each mouse received approximately 0.04 ml of the composition in their drinking water three times a day. Each mouse therefore received approximately a total of 0.04 x 3 = 0.12 ml of the composition from the drinking water each day plus 0.04 ml from the gavage, a total of 0.16 ml per day.

During the trial 4 mice from the experimental group and 5 from the control group died because of the gavage. The mice were all killed on day 17 and the tumours were dissected out and weighed. However, two tumours from the control group could not be removed for measurement because they were too extensive. The results are shown in Table 2.

Table 2

EXPERIMENTAL GROUP		CONTROL GROUP	
Mouse No.	Tumour Weight (g)	Mouse No.	Tumour Weight (g)
1	.10	20	.40
2	.10	21	.50
3	.20	22	.50
4	.20	23	.60
5	.20	24	.60
6	.30	25	.90
7	.30	26	.90
8	.40	27	.90
9	.40	28	1.00
10	.40	29	1.00
11	.50	30	1.00
12	.50	31	1.10
13	.50	32	1.10
14	.50	33	1.30
15	.50	34	1.30
16	.60	35	1.30
17	.70	36	1.50
18	1.00	37	1.70
19	1.70	38	1.80
Average tumour weight	0.48g	39	1.80
		Average tumour weight	1.1

It can be seen from Table 2 that the combined weight of tumours from the experimental group was 9.1 grams. The combined weight of the tumours from the control group was 21.2 grams. The control group tumour mass was therefore 21.2/9.1 = 2.32 times larger than the experimental group tumour mass.

Further, the average tumour weight in the control mice was 1.1 g. The average tumour weight in the experimental mice was 0.48g.

The average control group tumour mass is therefore 1.1/0.48 = 2.29 times larger than the average experimental group tumour mass.

The difference in the size of the tumours as measured by callipers during the trial is shown in Figure 5. It can be seen from Figure 5 that by day 17 the difference in size between the control and experimental tumours, as measured by callipers, is 8.8/3.6 = 2.44 times larger. Again there were no detectable side effects.

Professor Beverley has stated that this experiment has confirmed unequivocally that the treatment causes a statistically highly significant difference in tumour growth between the treated and control mice with no detectable side effects.

EXAMPLE 6

A 30lb 6 year old Manchester Terrier suffering from a spindle cell tumour was treated with the composition described in Example 1.

Before the treatment the animal had a hard lumpy swelling extending over the external side of the left foreleg from below the elbow joint up to the side of the shoulder. This diagnosis was made by Abbey Veterinary Clinics, London, who recommended amputation of the foreleg.

1cc of the composition was administered orally once a day for 5 days. By the end of 5 days the tumour had reduced in size considerably. The dose was then reduced to

1cc on alternate days for a further 7 days.

In addition, an extra 3 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 125mg per day.

A dietary regime was followed of organic fruits, organic vegetables, organic grains and lamb's liver to supply essential amino acids. Salt added to food was avoided.

Following the above treatment, the tumour disappeared. This result was certified by Mr. A. Sebesteny, head vet at the Imperial Cancer Research Fund, Clare Hall Laboratories.

EXAMPLE 7

A 60lb, 11 year old Doberman bitch was treated with a composition consisting of 30 mg copper orotate, 30 mg manganese orotate, 400 mg vitamin C and 3½ ml of an aqueous solution containing 350 mg sodium salicylate, prepared as in Example 1.

The animal was suffering from a urethral obstruction caused by an infiltrating malignant neoplasm thought to be a transitional cell carcinoma. This diagnosis was made at the department of Clinical Veterinary Medicine, Cambridge University. Before the treatment it could pass only a few drops of water with intense straining.

On the first day of treatment, the animal was given 2cc of the above composition (administered orally). On the second day it was given 2cc, followed by 1cc an hour later, then ½cc an hour after that. This was repeated every day for a week, after which time an improvement was noted. The dosage was then reduced to 2cc once a day for a further 3 weeks.

In addition, an extra 6 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 250 mg per day. A dietary regime as set out in Example 6 was followed.

Following the above treatment, the animal showed none

of the former symptoms. It was still alive and in excellent health 4 years after the treatment, as can be confirmed by its owner.

EXAMPLE 8

An 80lb, 6 year old Alsatian was treated with a composition consisting of 50 mg copper orotate, 50 mg manganese orotate, 50 mg zinc orotate, 400 mg vitamin C and 3½ ml of an aqueous solution containing 350 mg sodium salicylate, prepared in the same way as in Example 1, except that the zinc orotate was mixed dry in finely divided form together with the copper and manganese orotate.

The animal was suffering from a nasal tumour, thought to be a sarcoma and could not breathe through its nose. This diagnosis was made by the Department of Small Animal Medicine and Surgery, Royal Veterinary College, London. It had a large, hard, golf-ball sized swelling under the right eye.

It was given 2.6cc of the above composition, followed by 1.3cc an hour later (administered orally). This dose was repeated daily for 2 weeks by which time the tumour had significantly regressed, to the extent that the animal could breathe through its nose. The dosage was then reduced to alternate days for a fortnight, then to twice a week, then once a week.

In addition, an extra 8 g vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 330 mg per day.

A dietary regime as set out in Example 6 was followed.

By the end of the above treatment, the animal was symptom free. This result was certified by Mr. A. Sebesteny, head vet at the Imperial Cancer Research Fund.

EXAMPLE 9

A 60lb, 7 year old Doberman dog was treated with the

composition described in Example 7. It was suffering from carcinoma of the peritoneum. This diagnosis was made by the Department of Small Animal Medicine and Surgery, Royal Veterinary College, London. The animal was in an emaciated state, with a large swelling on the abdomen.

It was treated with 2cc of the composition, followed by 1cc an hour later (administered orally) every day for two weeks. After two weeks, the dosage was reduced to 2cc per day for a further two weeks, followed by a further reduction to 2cc on alternate days for another two weeks.

In addition, an extra 6 g vitamin C was administered orally each day and nicotinic acid was administered orally in an amount of 250 mg per day.

A dietary regime as set out in Example 6 was followed. After the above treatment the animal was symptom free, as can be confirmed by its owners.

EXAMPLE 10

A 150 lb human male around 45 years old, was treated with the composition described in Example 7. He was suffering from T-cell lymphoma, diagnosed at the Cromwell Hospital, London.

He was given 4.5cc of the composition (administered orally) once a day for 6 weeks (excluding Sundays). After this time, a regression was noted and the dosage was reduced to alternate days for 2 weeks, followed by a further reduction to once a week for three weeks.

In addition, an extra 15 g of vitamin C was administered orally every day and nicotinic acid was administered orally in an amount of 625 g per day.

A dietary regime as set out in Example 6 was followed.

Following the above treatment, all symptoms disappeared. He is still alive and well 6 years after the treatment.

CLAIMS

1. A composition comprising:

(a) a physiologically acceptable source of assimilable copper;

(b) a source of salicylic acid or a physiologically acceptable derivative thereof; and

(c) vitamin C and/or a physiologically acceptable source of assimilable manganese.

2. A composition according to claim 1, further comprising a physiologically acceptable source of assimilable zinc.

3. A composition according to claim 1 or 2 wherein the said metals are present in the form of salts with organic or inorganic acids.

4. A composition according to any one of the preceding claims in which components (a) and (b) are present as a copper salicylate complex.

5. A composition according to claim 3 wherein the salts are selected from orotates, aspartates, gluconates, tartrates, citrates, lactates and acetates.

6. A composition according to claim 3 wherein the salts are selected from chlorides, bromides, iodides, phosphates and sulphates.

7. A composition according to any of the preceding claims wherein the derivative of salicylic acid is sodium salicylate.

8. A composition according to any one of the preceding claims comprising:

(a) 15 to 60 parts by weight copper orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper orotate is used;

(b) 300 to 600 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other

than sodium salicylate is used; and

(c) 15 to 60 parts by weight manganese orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese orotate is used, and/or 200 to 1000 parts by weight vitamin C,

the parts by weight referred to being based on the total weight of these ingredient in the composition.

9. A composition according to claim 8, further comprising 5 to 20 parts by weight zinc orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc orotate is used.

10. A composition according to claim 8, comprising:

(a) 25 to 50 parts by weight copper oratate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable copper other than copper orotate is used;

(b) 300 to 600 parts by weight sodium salicylate, or equivalent amount of active ingredient when salicylic acid or a physiologically acceptable derivative thereof other than sodium salicylate is used; and

(c) 25 to 50 parts by weight manganese orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable manganese other than manganese orotate is used and/or 400 to 800 parts by weight vitamin C,

the parts by weight referred to being based on the total weight of these ingredients in the composition.

11. A composition according to claim 10, further comprising 5 to 15 parts by weight zinc orotate, or equivalent amount of active ingredient when a physiologically acceptable source of assimilable zinc other than zinc orotate is used.

12. A composition according to any one of the preceding claims for use in the treatment of the human or

animal body.

13. Use of a composition according to any one of claims 1 to 11 in the manufacture of a medicament for use in the treatment or prevention of a neoplastic disease.

14. Products containing:

(a) a composition as claimed in any one of claims 1 to 11; and

(b) vitamin C and/or one or more amino acid and/or nicotinic acid,

as a combined preparation for simultaneous, separate or sequential use in the treatment of neoplastic disease.

ABSTRACT

PHARMACEUTICAL COMPOSITIONS AND THEIR USE

A composition comprising:

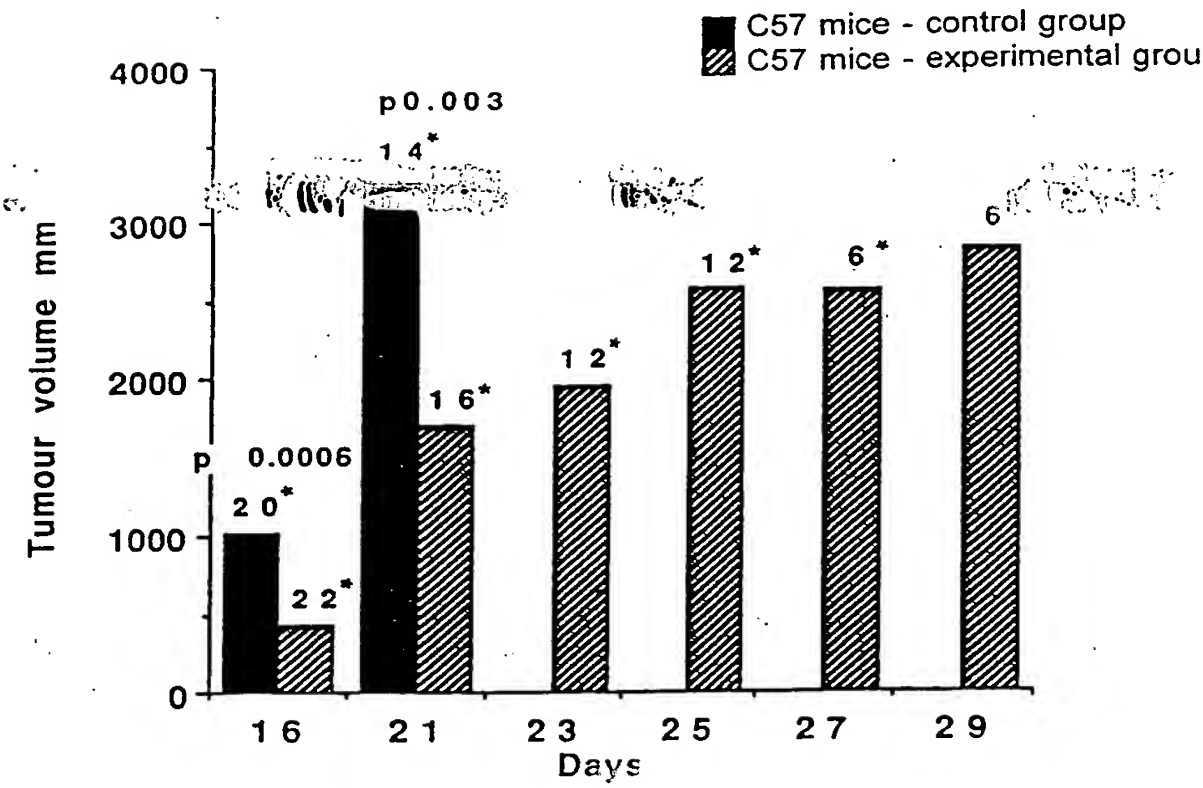
(a) a physiologically acceptable source of assimilable copper;

(b) a source of salicylic acid or a physiologically acceptable derivative thereof; and

(c) vitamin C and/or a physiologically acceptable source of assimilable manganese.

Figure 1. Growth of thymoma

Note that size of experimental tumours at late time points is artefactually small as those with the largest tumours have been killed



* No. of mice remaining

Figure 2

Weight of C57 mice

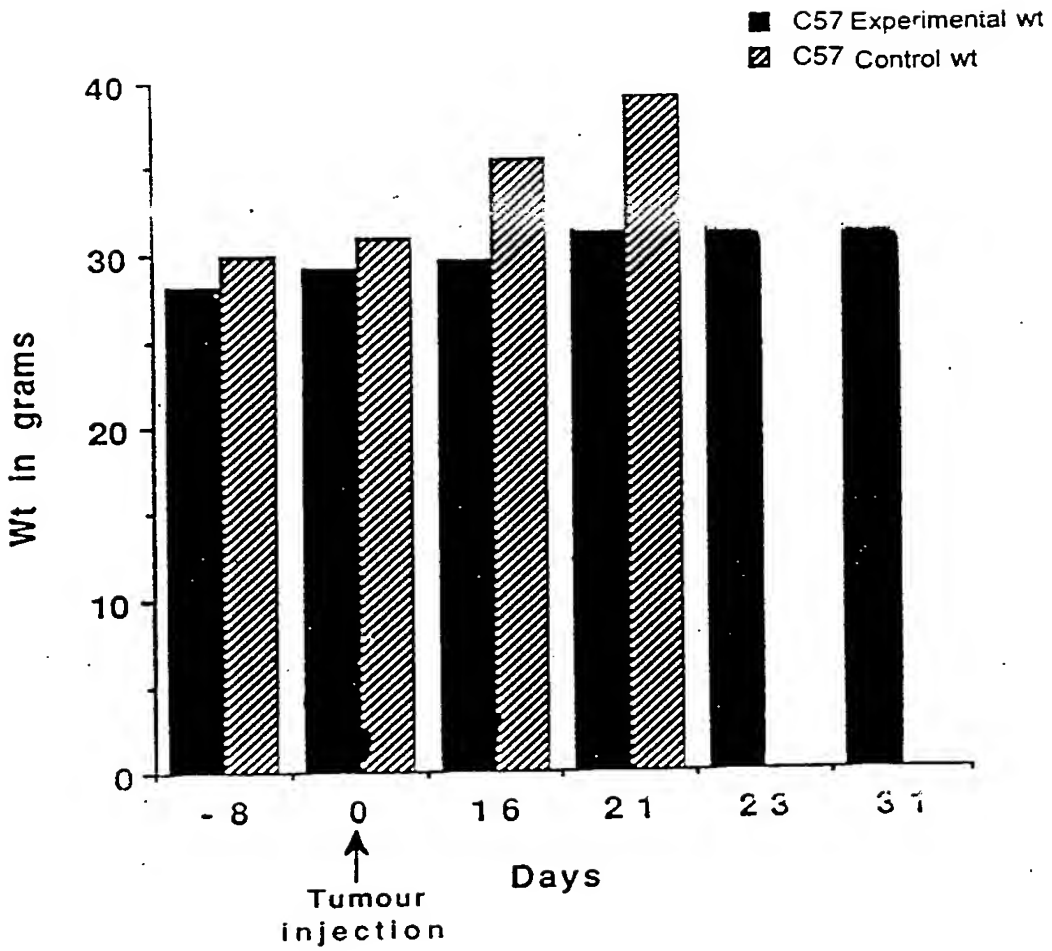
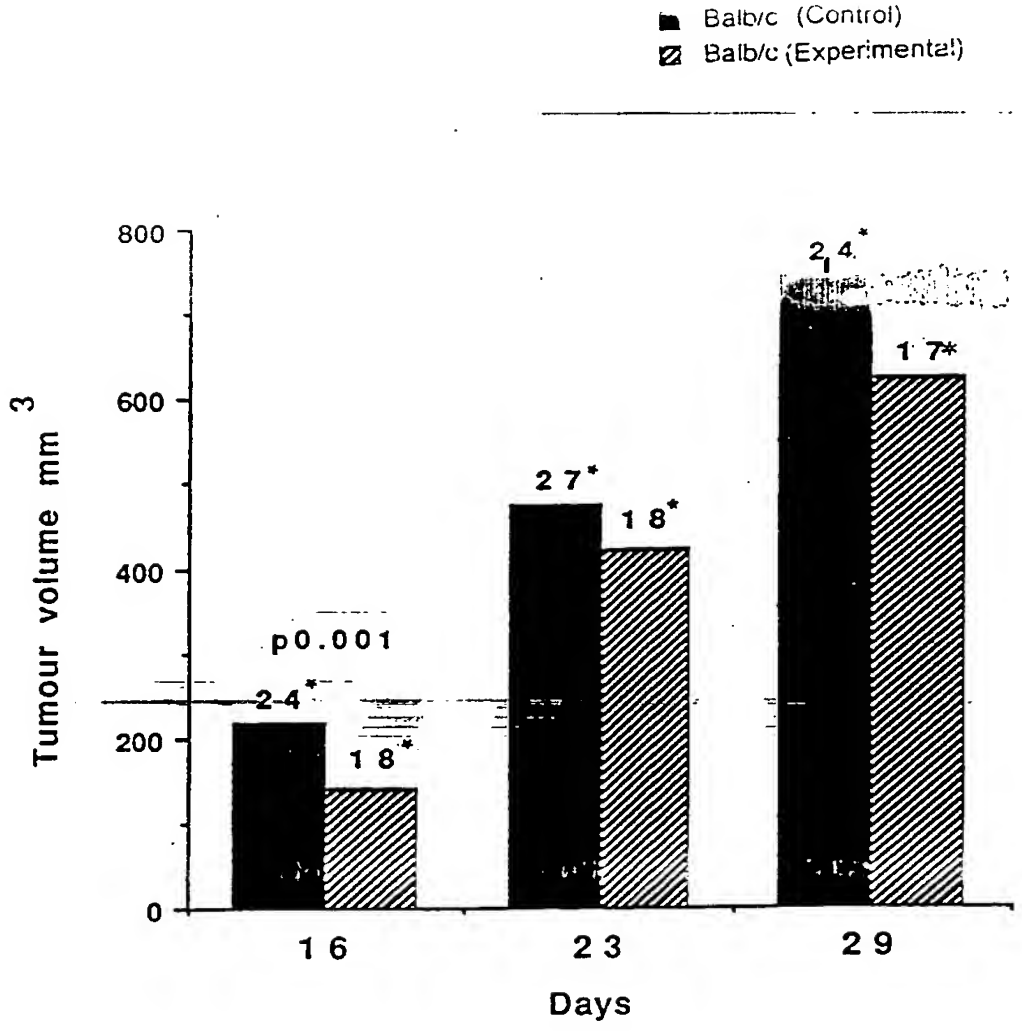


Figure 3. Growth of mammary carcinoma



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* Number of mice in group

Figure 4. Weight of Balb/c mice

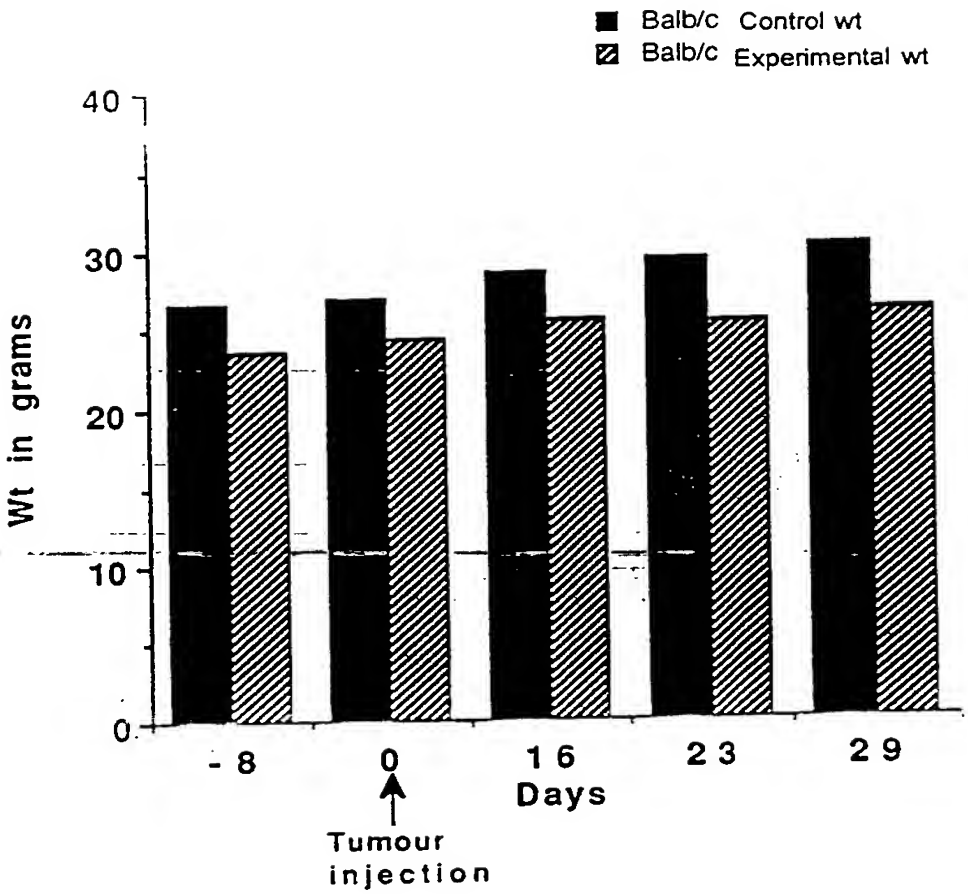
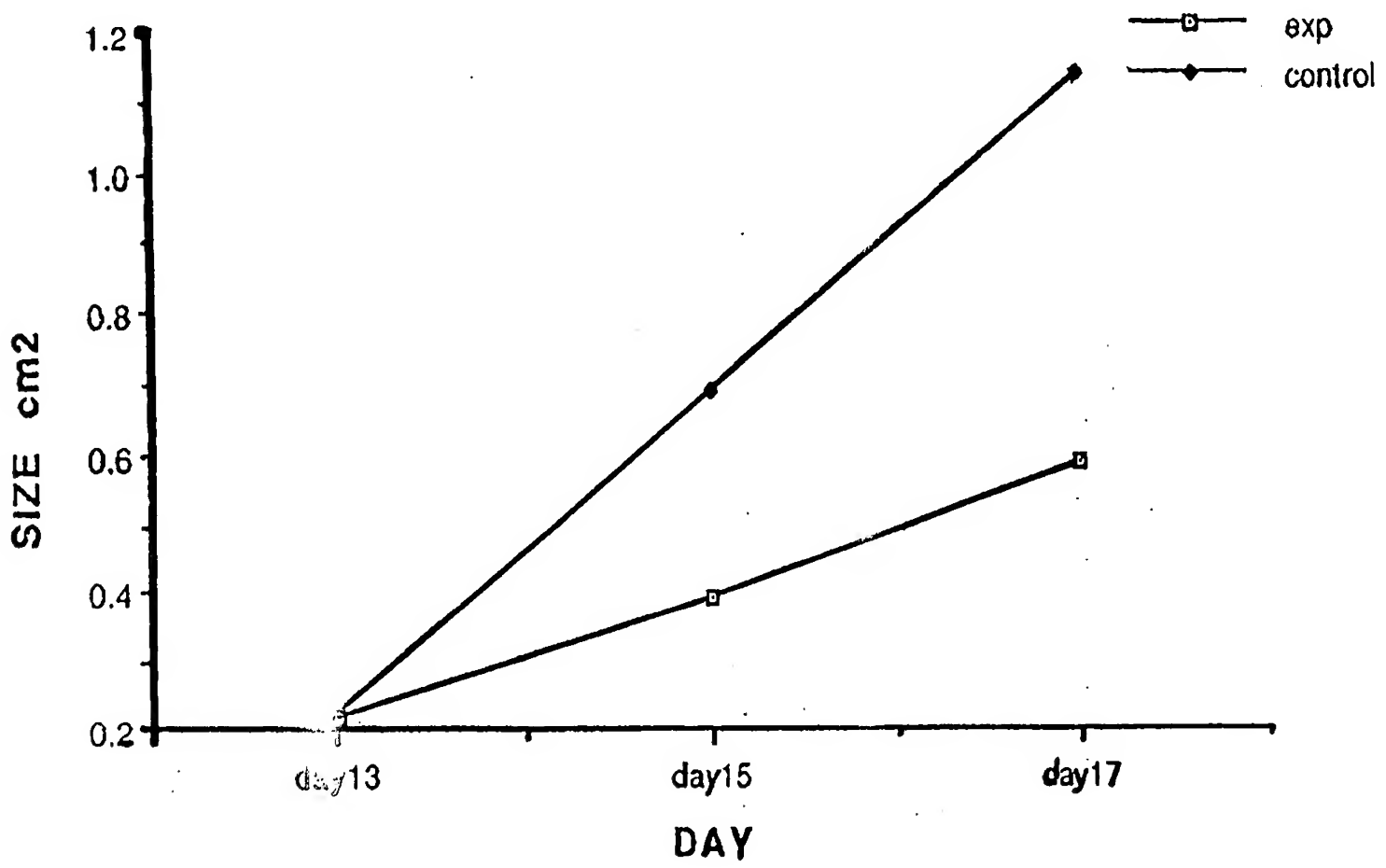


Figure 5

Growth of tumours (means)



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(Sarah Griffin)